REMARKS/ARGUMENTS

Status of the Claims.

Claims 1-5, 7-30, 38, and 53-56 are pending with entry of this amendment, with claims 6, 31-37 and 39-52 being cancelled and withdrawn from current consideration. Cancellation of these claims is without prejudice, without intent to abandon any originally-claimed subject matter, and without intent to acquiesce in any rejection or objection of record. Applicants expressly reserve the right to file one or more continuing applications containing these cancelled claims.

In the current Office Action, claims 1-5, 7-30, and 53-56 were rejected and claim 38 was allowed. Claims 3 and 4 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described so as to convey to one skilled in the art that Applicants possessed the claimed invention at the time of filing. Claims 6-8, 12-17, and 19-29 were rejected under 35 U.S.C. §103(a) as allegedly obvious in regard to Santa Cruz et al. (1996, PNAS, 93:6286-6290) in view of Ivanov (1997, Virology, 232:32-43) while claims 1-3, 5, 18, 30, and 53-56 were rejected under 35 U.S.C. §103(a) as allegedly obvious over Ivanov in view of Santa Cruz. Claims 9-11 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Ivanov et al.

Claims 3, 4, and 9 are amended herein. These amendments introduce no new matter and support for such is replete throughout the specification and claims as filed. The entry of such amendments is respectfully requested.

In regard to any rejection or objection remaining after entry of the current amendments, Applicants respectfully traverse each of such objections and rejections for the reasons explained below.

35 U.S.C. §112, First Paragraph.

Claims 3 and 4 were rejected under 35 U.S.C. §112, first paragraph. The claims were rejected as allegedly containing subject matter not described in the specification in a way as to reasonably convey to one skilled in the art that the Applicants possessed the claimed invention at the time of filing. Applicants herein amend.

The Office Action alleges that the specification is inadequate because it does not "disclose what is the core structure that is shared by these naturally occurring IRES and fragments for its function," and that since "the claims recite fragments of naturally occurring IRES, the specification needs describe a representative number of fragments of such IRES that has IRES function."

While Applicants believe unamended claims 3 and 4 are supported by the written description as filed, in order to further prosecution, such claims are amended herein to remove recitation of fragments of IRES. Since the language upon which the written description rejections were based is removed from claims 3 and 4, Applicants respectfully request that the rejections be withdrawn.

35 U.S.C. §103(a).

Claims 6-8, 12-17, and 19-29 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Santa Cruz et al. in view of Ivanov et al., while claims 1-3, 5, 18, 30, and 53-56 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Ivanov in view of Santa Cruz. Applicants respectfully traverse.

Three requirements must be met for a *prima facie* case of obviousness from combined references. First, there must be a motivation to modify the reference(s) or combine the teachings to produce the claimed invention. M.P.E.P. §2143.01. Second, there must be a reasonable expectation of success. M.P.E.P. §2143.02. Third, the prior art reference(s) must teach all of the limitations of the claims. M.P.E.P. §2143.03. Furthermore, the teaching or suggestion to combine, and the expectation of success, must both be found in the prior art and not based upon the disclosure of the Applicants. M.P.E.P. §2142. Applicants respectfully point out that these requirements have not been met for a *prima facie* showing of obviousness for any of the cited references or combinations thereof.

In regard to Santa Cruz in view of Ivanov, Applicants respectfully point out that such combination fails to meet the criteria explained above. First, and quite importantly, even assuming, *arguendo*, that all of the elements of the amended claims exist in the cited references, there is no motivation or expectation of success to combine the references. As explained by the M.P.E.P., the motivation and expectation of success must be supplied by the prior art, not by the current application. Also, M.P.E.P. §2143.01 states that the proposed modification to the prior art references cannot render such references as unsatisfactory for their intended purpose. Thus, "[i]f a

proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then **there is no suggestion or motivation to** make the proposed modification." M.P.E.P. §2143.01 citing In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Applicants strongly emphasize that the proposed modification of Santa Cruz by addition of IRES sequences would render Santa Cruz's constructs unsatisfactory for their intended purposes. For example, Santa Cruz clearly desires the production of the PVX.GFP-CP virions, which requires the presence of free coat protein subunits and fusion protein subunits. *See* abstract. Production of only fusion proteins and no free coat protein would not allow assemblage of virions because of steric hindrance (first paragraph of Results and Discussion on page 6287) but, quite importantly, production of free coat protein only, without the fusions, would not produce the desired virion assembly and spread throughout the plant. Thus, Santa Cruz specifically desires production of **BOTH** free coat protein and coat protein fusions. In fact, Santa Cruz specifically discusses methods to **DECREASE** the 2A cleavage of the fusions so that more fusion proteins remain. *See*, Results and Discussion page 6287 third paragraph. Therefore, increasing the cleavage of the constructs by use of IRES sequences (disregarding whether such would even work) would be detrimental and counterproductive to the goals of Santa Cruz. Contrary to the allegations of the Office Action, an ordinary artisan would **NOT** have been motivated to construct a PVX vector based on Santa Cruz in view of Ivanov to increase expression of the second protein in order to get more free protein because such would have been counterproductive to the stated goals of Santa Cruz. Again, as M.P.E.P. §2143.01 emphasizes, when the proposed modification of a reference is unsatisfactory for its intended purpose, then there is no suggestion or motivation to combine the references.

Thus, there is no motivation to combine the teachings of Santa Cruz with those of Ivanov. Therefore, *prima facie* obviousness has not been produced and Applicants respectfully request that the rejections be withdrawn.

In regard to Ivanov in view of Santa Cruz, applicants respectfully state that such combination also fails to produce *prima facie* obviousness. The Office Action does not give a motivation or suggestion for combination of Ivanov in view of Santa Cruz (as opposed to Santa Cruz in view of Ivanov). The mere conclusory statement that "sufficient motivation and expectation of success to reach the claimed invention" exits is not enough to establish *prima facie* obviousness. As stated in

the M.P.E.P., the "mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination." M.P.E.P. §2143.01 quoting In re Mills 916 F.2d 680. Additionally, a "statement that modification of the prior art to meet the claimed invention would have been " 'well within the ordinary skill of the art' . . . is not sufficient to establish a prima facie case of obviousness without some object reason to combine the teachings of the references." M.P.E.P. §2143.01 quoting Ex parte Levengood 28 USPQ2d 1300. To meet the burden of showing *prima facie* obviousness, a motivation/suggestion to read Ivanov in view Santa Cruz must be given (as well as a reasonable expectation of success).

Many points in the references themselves illustrate that there is no motivation to read Ivanov in view of Santa Cruz. For example, the construct systems used in Ivanov and Santa Cruz are quite different. Ivanov uses non-infectious plasmids *in vitro*, while Santa Cruz uses infectious vectors *in vivo*. Ivanov is allegedly concerned with production of separate proteins from separate translational events, while Santa Cruz deals with only partial production of separate proteins which are from the same translational event. Again, as pointed out above, Santa Cruz does not even desire totally separate protein production.

Furthermore, while Applicants note the Examiner's comments concerning Ivanov's discussion of the crTMV IRES and TMV U1 and agree that the sequences upstream of TMV U1 CP are not described as IRES by Ivanov, Applicants still strongly emphasize that Ivanov does indeed highlight the fact that IRES sequences in general are quite divergent and that the core functional areas of IREScp were not know by Ivanov at the time. *See*, e.g., Ivanov, page 40, 2nd col., last paragraph ("the boundaries of IREScp have not been defined," "IREScp sequences may contain," "[i]t remains to be investigated," etc., and page 42, 1st col., 2nd full paragraph (stating that IREScp is "markedly distinct" from IRESes of other sources described thus far and highlighting such differences). Ivanov's uncertainty as to the parameters of the TMV IREScp coupled with the fact that different viruses have different types of IRES sequences, supports Applicants' point that motivation to combine Ivanov and Santa Cruz (and reasonable expectation of success in doing so) does not exist. All of such points illustrate that there is no motivation to read Ivanov in view of Santa Cruz.

Additionally, notwithstanding the Office Action's lack of presenting motivation to read Santa Cruz in view of Ivanov or Ivanov in view of Santa Cruz, Applicants again emphasize that there is no

expectation of success in combining the two cited references. As with motivation to combine, the expectation of success must be found in the prior art and not be based on the Applicants' disclosure. M.P.E.P. §2142. Again, the prior art cited does not show any reasonable expectation of success for combination. In fact, as explained for lack of motivation to combine, Ivanov and Santa Cruz are quite dissimilar in content and aim, so an expectation of success in combining them would not arise. For example, Ivanov is focused on an *in vitro* system while Santa Cruz is focused on an *in vivo* system. There is quite a degree of unpredictability which would arise in combination of the two systems. Such unpredictability argues against a reasonable expectation of success in their combination. The office action assumes that elements of the constructs of Santa Cruz will easily work in an operable system with the plasmids of Ivanov (and *vice versa*). However, what can be done *in vitro* (as in Ivanov) is often different than what can be done *in vivo* (as in Santa Cruz) and different considerations must be taken into account for each situation. For example, Ivanov merely has *in vitro* translation of sequences from its plasmids. On the other hand, an *in vivo* vector would need to also, e.g., replicate, assemble intact virus-like particles or viruses, optionally retain infectivity and optionally spread in a plant, etc. Many potential problems can obviously arise in construction/design of *in vivo* constructs, e.g., degradations, inactivations of vectors and/or gene products, etc. Thus, there is unpredictability in moving elements from one construct system to another and no reasonable expectation of success in doing so.

Furthermore, the two methods differ greatly in their translation strategies, namely, Ivanov uses IRES sequences having multiple translation events while Santa Cruz uses a single translation event with cleavage of a fusion protein. Also, Ivanov acknowledges the distinctness of various IRES sequences (*see* above). Due to the disparities in the systems, there is no reasonable expectation that the addition of an IRES sequence from Ivanov to Santa Cruz's structures would give better results. In fact, as explained above, such combination would be counterproductive.

Applicants submit, *arguendo*, that at the very most it is an invitation to experiment with different IRESes in different constructs (i.e., creation of constructs with IRES and construct backbone from different origins) to see what results would occur. Because the two references do not present an expectation of success, the rejection should be withdrawn.

Thus, since the references do not present, either singly or combined, all three required elements, a *prima facie* case of obviousness under §103(a) has not been met. Applicants therefore respectfully request that the rejections be withdrawn.

35 U.S.C. §102(b).

In the current Action, claims 9-11 were rejected under 35 U.S.C. §102(b) as being anticipated by Ivanov et al. (1997, Virology, 232:32-43). Applicants respectfully traverse.

Applicants respectfully point out that Ivanov cannot anticipate the current claims because Ivanov does not include all the limitations of the current claims. In order for a reference to anticipate a claim M.P.E.P. § 2131 requires that all elements of the claim(s) in question be present in the cited reference:

> A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. (M.P.E.P. §2131 citing Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631 (Fed. Cir. 1987)).

Additionally, "every element of the claimed invention must be identically shown in a single reference," and the "elements must be arranged as in the claim under review." *See*, In re Bond, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). Applicants respectfully point out that Ivanov does not meet these requirements.

The Office Action alleges that Ivanov discloses:

> a vector, pHΔβNPTCP *(sic)*, which comprising a T7 promoter, inverted tandem repeat, β-sequence of potato virus X, a nucleic acid encoding neomycin phosphotransferase I gene, the **IREScp**, and the Coat protein (CP) gene of the crTMV. (Office Action at page 8, quoting Ivanov at page 33, 2nd col., 4th paragraph, lines 3-14 and Figure 4; emphasis added).

The Action also alleges that Ivanov teaches, "a vector comprising a stable stem loop structure 5' to the IRES, wherein this structure blocked the expression of CP protein expression." *See* Office Action at page 8, quoting Ivanov at page 39, 1st col., lines 1-5 and Figure 7A-C.

The Office Action characterizes unamended claims 9-11 of the current application as being drawn to IRES capable of directing the expression of an internal ORF in a heterologous viral vector, and states that "[a]lthough the function of the crTMV IREScp for directing expression in heterologous viral vector is not discussed in the reference, it is the inherent function for said IRES because it has the same structure as the claimed IRES."

Applicants respectfully point out that notwithstanding such passages from Ivanov, the Office Action has not met its required burden in presenting anticipation of claims 9-11. Ivanov does NOT contain an IRES capable of directing the expression of an internal ORF in a heterologous plant viral vector.

For example, while crTMV IRES sequences are given in Ivanov, the Office Action cites to two locations (*see above*) to support the contention that such IRES are ones capable of directing the expression of an internal ORF in a heterologous plant viral vector. However, the Action is mistaken in its characterization of the plasmids on page 33 of Ivanov. The description of pHβΔNPTCP on page 33 clearly states that the construct "contain[s] no crTMV-derived sequence upstream from the initiation codon of the CP gene." Thus, the construct contains no IRES sequences.

Furthermore, the constructs on page 39 of Ivanov are not heterologous plant viral vectors. Thus, Ivanov also fails to anticipate the current invention because the plasmids of Ivanov are not equivalent to the recombinant plant viral vectors of the instant claims. The Office Action uses the term "vector" too generically in its analysis. For example, the claims of the present invention are drawn to a heterologous plant viral-based vector, while Ivanov is drawn to various non-infectious plasmids. As is clear from the specification, the current plant viral vectors (with IRES, etc.) are optionally used to replicate in plants and to infect plants *in vivo* and, in particular cases, to systemically spread throughout a plant. The present invention comprises plant viral vectors comprising, e.g., "modified virus capable of expressing a desired protein or trait in a host." *See*, e.g., page 6, lines 4-5. This is as opposed to Ivanov which comprises plasmid constructs to be used *in vitro*, which might contain some viral genes in their sequence. The differences between the two approaches will clearly be appreciated. Additionally, the coat proteins in the Ivanov plasmids are from crTMV as are the IRES sequences (i.e., they are not heterologous to one another). *See*, e.g., last 2 lines of text on page 38 through end of 1st column of page 39.

Applicants note that claim 9 is amended herein to read a "heterologous plant viral-based vector" in order to more fully delineate the parameters of the currently claimed embodiments. Support for such change is located at, e.g., paragraphs 1 and 25, etc. Entry of the amendment is respectfully requested.

Thus, because Ivanov does not contain a construct comprising an IRES sequence capable of directing the expression of an internal ORF in a heterologous plant viral vector it does not teach every element of the current claims, and so cannot anticipate the current claims. Applicants, therefore, respectfully request that the rejections be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3507.

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